UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,913	10/20/2003	Rudolf Wank	104341.B090019	2270

23911 7590 08/07/2009

CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
08/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,913	WANK, RUDOLF	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

   Applicant's amendment and remarks field June 17, 2009 have been considered.

   Claims 1-28 and 36-44 have been canceled.

   Claims 29, 32, 33 and 35 have been amended.

   Claims 29-35 are pending.

   Upon further consideration, the election of species requirements pertaining to:

   I. the "agent or a single combination of agents that activate T-cells that will be used in the first step," and

   II. the "agent or a single combination of agents that activate T-cells that will be present after the addition of naïve PBMC to the cells stimulated in the first step,"

   have been withdrawn.

   Thus, claims 29-35 are under examination wherein the elected sources of PBMCs for the first and second PBMC method steps of the invention are derived from a single cancer patient donor and the elected type of cancer to be treated is breast carcinoma.

2. This Office Action is in response to applicant's amendment and remarks field June 17, 2009.

   The previous rejections of record can be found in the Office Action mailed January 17, 2009.

   The previous objections to the specification have been withdrawn in view of applicant's amendment to the claims.

   The previous rejection under 35 USC 112, 2nd paragraph has been withdrawn in view of applicant's amendment to the claims and applicant's argument.

   The previous rejection under 35 USC 112, 1st paragraph has been withdrawn in view of applicant's amendment to the claims.

The previous rejections under 35 U.S.C. § 103(a) have been withdrawn upon further consideration and in view of applicant's amendment to the claims.

New Grounds of Rejection are put forth below.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 29-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29, and dependent claims thereof, recites "wherein the primary stimulation and/or the activation of naive PBMC occurs in the presence of at least one cytokine selected from the group of interleukin-2…." There are two indefinite aspects to this wherein clause. First, it is unclear if "wherein the primary stimulation" refers to step (a) of the claimed method or something else having to do with the naïve PBMC, i.e., "wherein the primary stimulation…of naive PBMC," or perhaps both simultaneously? Second, the phrase "wherein…the activation of naive PBMC" lacks antecedent basis in steps (a)-(e) of the claim.

One way of addressing this issue would be to amend the claim to say something like "wherein the primary stimulation of step (a) and/or the stimulation of naive PBMC of step (d) occurs in the presence of at least one cytokine selected from the group of interleukin-2…"

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 29 and 31 are rejected under 35 U.S.C. 102(e) as being anticipated by Michael Gruenberg (US 2003/0175272 A1).

Gruenberg teaches a method for treating cancer comprising stimulating PBMC with immobilized anti-CD3 and IL-2, and then restimulating said PBMC with a second addition of naïve PBMC followed by intravenous administration to the cancer patient (see, e.g., page 1,

paragraph [0011]; page 2, paragraphs [0014]-[0015] and [0025]; page 3, paragraph [0033]; page 5, paragraph [0060]; page 7, paragraph [0089]; page 10, Example 4; and claim 5).

Thus, Gruenberg anticipates the claimed invention.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 29-32, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teruaki Sekine (0 409 655 A2) in view of Flyer et al. (WO 97/32970).

Sekine teaches the goal of adoptive immunotherapy is to treat a wide variety of human cancers by administering immunologically active cells to the patient. However, according to Sekine, "one major drawback to such immunotherapy is the difficulty in obtaining the large numbers of cells that would be required for such treatment." (see page 2, 2nd paragraph). To this end, Sekine teaches a method for preparing cells for adoptive immunotherapy comprising stimulating patient derived PBMC with immobilized anti-CD3 antibodies, followed by a second step where the cells and culture media are transferred to a culture environment lacking anti-CD3 antibodies, and finally a third step where a T cell mitogen, such as IL-2, is added (see, in particular, page 4, 1st paragraph and the paragraph bridging pages 4-5 through page 5, 2nd paragraph). Sekine further teaches intravenous administration of their immunologically active cells to treat various human cancer patients in conjunction with radiotherapy (see page 5, 5th and 6ht paragraphs and page 7).

Sekine differs from the claimed invention in that it does not explicitly teach adding naïve PBMC to the patient derived PBMC stimulated with immobilized anti-CD3 antibodies, it does not explicitly teach the treatment of breast carcinoma or the various dosages recited in the instant claims and it does not teach administering to a patient a combination of 1. naïve PBMC and patient derived PBMC stimulated with immobilized anti-CD3 antibodies and 2. CD3-activated cells.

However, Flyer teaches that a cell culture containing naïve PBMC and immobilized anti-CD3 antibodies will produce T cell mitogens and co-stimulatory functions that potently activate the proliferation of patient derived PBMC (see, in particular, page 22, 2nd-3rd paragraphs and page 21, 1st paragraph; page 24, 2nd-3rd paragraphs; page 25, 1st paragraph; pages 37-38, part B; paragraph bridging pages 40-41).

Thus, given the reference teachings it would have been obvious to one of ordinary skill in the art that either the third, or the second and third steps of Sekine could be favorably supplanted

by a single step comprising incubating the anti-CD3 stimulated patient derived PBMC with naïve PBMC in the presence of immobilized anti-CD3 as taught by Flyer. One of ordinary skill in the art would expect such a procedure to induce superior T cell proliferation compared to the use of selected T cell growth inducing cytokines alone, such as IL-2, given the ability of activated PBMC to provide co-stimulatory signals and a diversity of T cell growth promoting cytokines.

As to the particular dosage limitation recited in the instant claims and treatment of the elected species of cancer, breast carcinoma, according to the claimed method, Flyer teaches how the dosing and route of administration of immunotherapeutic T cells is a results effective variable subject to routine optimization and further (see paragraph bridging pages 31-32). Moreover, consistent with the teachings of Sekine, Flyer teaches that adoptive immunotherapy is useful for treating tumors in general (see page 2, 1st paragraph and page 4, 2nd paragraph). Based on the teachings of the Sekine and Flyer, and filtered through the general knowledge in the art, one of ordinary skill in the art would have had no particular reason to think that adoptive immunotherapy would not be successful for the treatment of, e.g., breast carcinoma.

In the recent court decision KSR International Co. v. Teleflex Inc., the U.S. Supreme court determined that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007).

Since there is a desire in the market for breast carcinoma treatments, applying the method of treating cancer taught by Sekine and Flyer to the treatment of the species of cancer which is breast carcinoma represents a predictable logical step that a person of ordinary skill in the art would have good reason to pursue as a known option within his or her technical grasp.

Thus, one of ordinary skill in the art would have been motivated and would have reasonably expected to be able to treat breast carcinoma according to the claimed method.

Lastly, with respect to claim 35 which recites "the method of Claim 29, wherein administering the CAPRI cells further comprises: administering CD3-activated T cells," this claim, given its broadest reasonable interpretation consistent with the instant specification reads on performing the method of claim 29, and further isolating T cells produced by practicing the method of claim 29 and then administering said cells to the patient. However, it would have been obvious to one of ordinary skill in the art to do so given that as the combination of Sekine and Flyer make clear, it is the T cells contained within the PBMC which have the dominate role in killing the patient cancer cells. Therefore, isolating the

cancer killing T cells and administering them in addition to the PBMC mixture would have been obvious to one of ordinary skill in the art.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments put forth in their Remarks filed June 17, 2009, insofar as they are germane to the New Grounds of Rejection put forth above are addressed below.

Applicant argues the mechanism hypothesized by Wank/the instant specification by which PBMC are stimulated according to the claimed method makes the claimed method distinct from the prior art. Applicant further argues the present invention "uses the primary stimulated PBMC to stimulate the naive PBMC and no supplemental stimulating agents are required (pg. 4, lines 9-24)." Applicant further argues "because the method in *Babbitt et al.* results in an internalization of both CD3 and αβ TCR, which would prohibit the activation of naive PBMC T cells via the αβ TCR, one skilled in the art would not look to *Babbitt et al.* for motivation to produce effector T cells via αβ TCR stimulation." Lastly, applicant argues evidence of unexpected results in that "the method according to the present invention for treating cancer using CAPRI cells was surprisingly found to be far superior to the method of using CD3-activated PBMC to achieve cancer cell lysis as disclosed in *Babbitt et al.,* and *Gold et al.* More specifically, a nearly complete lysis of autologous cancer cells by CAPRI cells was observed, while the CD3-activated PBMC showed no significant lytic activity (see attached Figure 1)."

Many of applicant's arguments are echoed in the Declaration of Dr. Wank also submitted June 17, 2009.

In the interest of compact prosecution, it will be assumed that applicant would make similar, if not the same, arguments with respect to the instant rejection.

Applicant's arguments in conjuction with the Declaration of Dr. Wank have been considered but have not been found convincing.

With respect to applicant's arguments concerning the mechanism hypothesized by the Declaration of Dr. Wank/the instant specification by which PBMC are stimulated according to the claimed method, although the reference teachings do not explicitly teach the same mechanism of PBMC stimulation, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

With respect to applicant's argument that the claimed method "uses the primary stimulated PBMC to stimulate the naive PBMC and no supplemental stimulating agents are required," applicant appears to be arguing a limitation not claimed in that the wherein clause of base claim 29 appears to encompass in its breadth the use of supplemental stimulating agents at each of the claimed steps.

With respect to applicant's argument that because the method in *Babbitt et al.* results in an internalization of both CD3 and αβ TCR, this would prohibit the activation of naive PBMC T cells via the αβ TCR and thus, one skilled in the art would not look to *Babbitt et al.* for motivation to produce effector T cells via αβ TCR stimulation, applicant has not provided objective evidence demonstrating that the method of Babbitt "results in an internalization of both CD3 and αβ TCR." Moreover, the instant claims are not limited to a method for producing "effector T cells via αβ TCR stimulation."

With respect to the alleged evidence of unexpected results when the claimed invention is compared to "conventional CD3 activated cells" as stated on page 3, Section 8 of the Wank Declaration, this is not found convincing because applicant does not appear to have compared the claimed invention to the closest prior art which was Babbitt or Gold. More particularly, looking at the materials and methods section of Dr. Wank's manuscript included with the Declaration, the protocol of Babbitt or Gold does not appear to have been followed with respect to preparing CD3 stimulated PBMC, i.e., applicant did not (a) culture PBMC isolated from a cancer patient with anti-CD3 antibodies and IL-2 (b) remove the cell culture supernatant (referred to as "T3CS" by Babbitt) (c) obtain a second population of peripheral-blood mononuclear cells (PBMC) from the same cancer patient and (d) expose said second population of PBMC to the T3CS cell culture supernatant.

9. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Teruaki Sekine (0 409 655 A2) in view of Flyer et al. (WO 97/32970) as applied to claims 29-32, 34 and 35 above, and further in view of Gale Granger (5,837,233, of record) and Johnson et al. (5,217,704, of record).

The teaching of Sekine and Flyer are given in Section 8 above.

Sekine and Flyer do not explicitly teach administration of activated PBMCs directly into the tumor of the patient when the tumor is less than 0.5 cm.

However, Granger teaches a method of treating various human tumors comprising incubating PBMCs obtained from the cancer patient with allogeneic donor PBMCs ex vivo and then administering the cells directly into the tumor. (see, in particular, columns 10-11 and Examples 1-3). Granger further teaches that cytokine production directly within a tumor can induce tumor regression and that intralesional administration of immunotherapy is considered to be safer than systemic administration (see, in particular columns 1-3).

Moreover, Johnson teaches that "imaging of small, malignant lesions in a human subject in order to treat or cure the malignancy is a prime objective in current cancer treatment. If a malignant lesion or tumor can be detected at a very early stage, treatment through surgery, chemotherapy, radiation or other methods can be performed…the present invention images small malignant lesions with tumor masses from about 0.5 cm in diameter." (see, in particular, column 27, 2nd paragraph).

Thus, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat cancer by administering activated PBMCs generated according to the teachings of Sekine and Flyer directly into a small tumor, such as tumor of about 0.5 cm. In particular, given that it is easier to treat a small tumor than a larger tumor as is well known by one of ordinary skill in the art and as is echoed by Johnson, and further given that as taught by Granger intratumor administration of T cells expressing cytokines can induce tumor regression and has safety benefits over systemic administration, one of ordinary skill in the art would have been motivated to treat cancer by administering activated PBMCs generated according to the teachings of Sekine and Flyer directly into a small tumor, such as tumor of about 0.5 cm.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claim is unpatentable over Sekine in view of Flyer, Granger and Johnson.

Applicant's arguments put forth in their Remarks filed June 17, 2009, insofar as they are germane to the New Grounds of Rejection put forth above are addressed below.

Applicant argues the invention results in dendritic cell maturation which is allegedly an unexpected result compared to the teachings of Granger and Johnson. Applicant further argues that cells generated according to the claimed method surprisingly enhance HLA class I and II surface expression on epithelial tumor cells which is "a deciding factor of the high cytotoxic capacity of Capri cells against cancer cells…these results obtained...are superior and unexpected over the disclosures and teachings of Granger and Johnson...".

Many of applicant's arguments are echoed in the Declaration of Dr. Wank also submitted June 17, 2009.

In the interest of compact prosecution, it will be assumed that applicant would make similar, if not the same, arguments with respect to the instant rejection.

Applicant's arguments in conjuction with the Declaration of Dr. Wank have been considered but have not been found convincing.

Applicant's arguments are not found convincing because applicant is not comparing the results of practicing the claimed invention to the nearest prior art, which previously was Babbitt and Gold.

Moreover, even if applicant has discovered for the first time new mechanisms by which the claimed method acts to treat cancer, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Furthermore, one of ordinary skill in the art would have been motivated to practice the claimed method and would have had a reasonable expectation of success in doing so for the reasons given in the prima facie obviousness rejection put forth above.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644